CHAPTER 9

Programming Hypertension—Animal Models: Causes and Mechanisms

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Abstract

Hypertension can be programmed by experimental manipulation of the intrauterine environment. Studies to date suggest that, at least in some models, common pathways such as glucocorticoids or the renin-angiotensin system cause programming of arterial pressure. How mechanisms involved in controlling "normal" arterial pressure have been altered, remains a largely unanswered question, though the process may include the programming of the major organs and endocrine/neural systems involved in long-term blood pressure regulation. Clear evidence demonstrates a prominent role for the programming of the kidney in the development of hypertension. The major mechanisms examined to date include a reduced nephron endowment and alterations to the function of renal renin-angiotensin system. These studies do not preclude a role for other major cardiovascular organ systems (brain, vasculature, heart) in the programming of hypertension. Several studies have identified sex-specific differences in the programming of hypertension, which may relate to fetal sex-specific rates of placental gene expression and/or sex-specific timing of fetal development. Future studies should be directed towards examining the integrative control of blood pressure in prehypertensive animals to differentiate between the primary initiating programming events and events secondary to the development of hypertension. Understanding the mechanisms involved will be essential for devising preventative and/or treatment strategies.

Introduction

High blood pressure affects 20% of adults and is a major risk factor for cardiovascular diseases such as stroke, myocardial infarction, peripheral vascular disease and chronic renal failure.[1,2] In the majority of cases, the cause of the hypertension is unknown, with less than 10% of cases accounted for by secondary (i.e., renal artery stenosis, adrenal tumour) or genetic factors. Recently, attention has shifted to the idea that adult hypertension can be programmed in utero.[3] It is hypothesised that an adverse intrauterine environment during critical stages of development permanently alters, or 'programmes' the development of fetal tissues, which enables the fetus to survive, but with adverse consequences in postnatal life.[3] The mechanisms by which an altered intrauterine environment might exert these effects may involve epigenetic effects in the embryo/fetus (discussed elsewhere in this book, Chs. 6, 7).

Here we will briefly outline animal models of adverse intrauterine environments that have been demonstrated to lead to adult hypertension. However, our primary focus will be to explore, where evidence is available, the organs and physiological systems that may be affected and thus underlie the development of hypertension (Fig. 1). A clearer understanding of these

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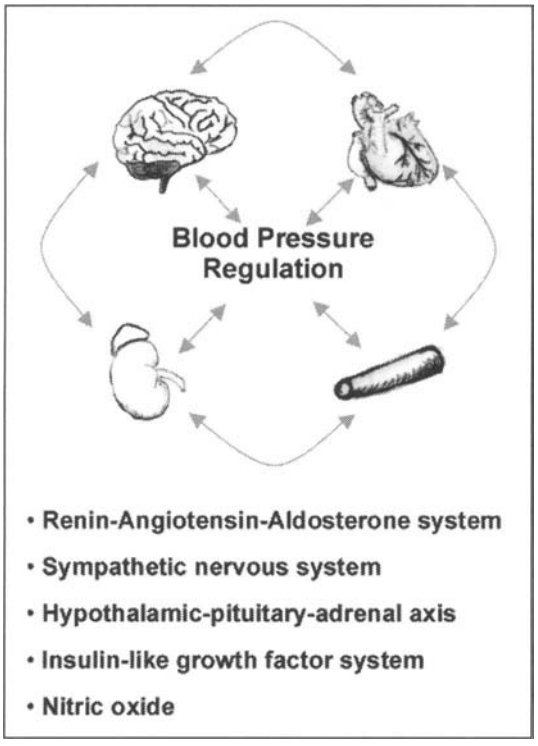

Figure 1. Schema suggesting possible targets for the programming of hypertension.

mechanisms and the delineation of possible common pathways, such as glucocorticoids for which there is strong evidence,[4,5] may ultimately lead to potential treatments or strategies for prevention of programmed hypertension.

Models of Arterial Pressure Programming

There is now compelling evidence to support the hypothesis that events occurring during fetal life can have life-long consequences for the health of the adult. The first models centred on producing low birth weight via maternal nutrient restriction, in line with the original hypothesis that low birth weight was associated with high blood pressure.[6,7] With an increasing understanding of the mechanisms of fetal programming, models have become more specific, examining the impact of micro-nutrient deficiencies, hormones, and conditions that are common in human pregnancy, such as anaemia and hypertension. Attention has also begun to focus on critical windows during development when different organs have a greater susceptibility to programming.[8]

Arterial Blood Pressure

In considering the topic of programming of blood pressure, it is timely to evaluate the methodologies associated with its measurement.[9,10] The most significant factor is whether blood pressure is measured directly, that is via an indwelling arterial catheter, or indirectly via tail-cuff. This is an important consideration for two reasons: (1) the degree of stress associated with each method and (2) the length of time over which the measurement is made varies considerably. Thus, whilst the tail-cuff method can provide reliable measurements and is the most frequently used method in rats (see Table 1), for reasons that will be discussed, direct measurement of blood pressure, preferably by telemetry, is the gold standard.

Table 1. Different methodologies used to measure blood pressure in models of "programmed" hypertension

Anaesthetised	Intra-arterial			Rat [20,28,29,31-33,143]
				Sheep [30,143]
Conscious	In-direct	Restrained	[1]Single period	Rat [16-21,24,25,42,43,45,77,78,110]
			Intermittent	Rat [22,23,27,36-38,44,56,60,105,106]
Conscious	Intra-arterial	Restrained	[2]"Awake"	Rat [35,92,130,131,139,140]
			[3]Single period	Rat [74,93,95]
			or intermittent	Rabbit [53]
			(recovered)	Sheep [15,40,80,128,135,144]
			24-hour	Sheep [76,90,113,129]
Conscious	Intra-arterial	Unrestrained	Intermittent	–
		(telemetry)	24-hour	Rat [11-14]

Conscious unrestrained 24-hour telemetry recording is the gold standard. [1]Single period (tail-cuff)—blood pressure measurements taken at a single time-point. [2]"Awake"—refers to those studies that did not allow the animals to fully recover from the surgical implantation of catheters before blood pressure was measured (minimum of 3 days). [3]Single period or intermittent (intra-arterial)—blood pressure recorded for a short period (hours) on a single day or over days to weeks, (minimum 3 days recovery from surgery). The [numbers] are references cited in this review using each method

Telemetry offers long-term, 24 hour intra-arterial blood pressure recording in conscious unrestrained, and thus unstressed, animals. Further, it allows for analysis of day versus night pressures and, due to the sensitivity of the technique, small differences in blood pressure can be detected (~5 mmHg). Unfortunately, the high cost associated with telemetry means that for long-term studies, such measurements are not always practicable. Indeed, whilst telemetry is common in the field of hypertension in general, only a handful of studies to date have used telemetry to examine the in utero programming of hypertension.[11-14] Chronic indwelling catheters in the carotid and femoral arteries also provide quality measures of blood pressure in rodents and larger animals. An advantage of this technique is that blood sampling can be performed in addition to measurement of blood pressure and supplemented with a venous catheter, allows for concomitant infusion of agents such as antihypertensives. However, the presence of externalised catheters does add an element of restraint stress. Further, the practicality of this technique for long-term studies is limited by the ability to maintain catheter patency for longer than a few weeks. Due to the invasive nature of both these techniques it is critical that the animals are given the appropriate length of time to recover from surgery before measurements of blood pressure begin.[9] Unfortunately, studies in animals equipped with indwelling catheters often fail to take full advantage of the benefits conferred, still only measuring blood pressure for short periods. For example, sheep from undernourished mothers demonstrated elevated morning blood pressure prior to, but not after feeding. The question remains as to whether these animals had significant hypertension or not; 24-hour recordings of blood pressure would have given a more accurate picture.[15]

Tail-cuff plethysmography allows blood pressure of rodents to be followed long-term within animal, but only measures single-time point systolic blood pressure accurately and the animals are subject to the stress of restraint. The element of restraint stress can be minimised in rats with training; however, as mice fail to show significant training, tail-cuff measurements in mice are questionable.[10] Another important consideration is that an adverse intrauterine environment may not alter blood pressure per se, but rather the blood pressure response to stresses such as restraint. Therefore if elevations in blood pressure detected by tail-cuff occur in the absence of left ventricular hypertrophy, an indicator of increased after-load with elevated blood pressure, blood pressure should be confirmed intra-arterially (preferably by telemetry) before concluding

the stimulus has programmed hypertension. There are considerable disadvantages with measurements, such as those obtained by tail-cuff, that are of only a single time-point, or collection of direct, intra-arterial measurements for only short periods each day. These measurements, taken predominantly during the day, can be affected by factors such as feeding, the particular time of the day in relation to diurnal rhythm, and presence or absence of other activity in the room during recording. This is especially significant for rodents that are nocturnal as blood pressure during the day is considerably lower, and thus small differences in blood pressure that may be evident during night-time might not be detectable during the day-time. In the clinic it is the widely accepted practice not to make judgments about the significance of raised blood pressure until at least three measurements have been taken over a period of weeks, since anxiety, stress or discomfort can temporarily increase blood pressure of people who do not have significant hypertension. Yet, the majority of animal studies examining the impact of an adverse intrauterine environment on adult blood pressure, particularly those in rodent models, utilised tail-cuff plethysmography to determine blood pressure often only on a single day (Table 1).

Tonkiss and colleagues, who used telemetry to measure blood pressure in offspring of dams malnourished during pregnancy, presented a telling example of these drawbacks.[14] Previous studies in this model, based on indirect tail-cuff blood pressure measurements, demonstrated increases in systolic blood pressure of greater than 20 mmHg in the offspring of malnourished rats.[16-27] However, Tonkiss et al demonstrated a much more modest increase in blood pressure (+4 mmHg in diastolic pressure during the night) and provided evidence that the responsiveness to stress was augmented in prenatally malnourished rats.[14] Indeed, this study strongly suggests that the stress associated with the tail-cuff procedure, contributed to the large elevations in blood pressure seen previously in this model. However, these differences may also reflect the importance of protein contect and overall composition of a diet to programming of hypertension (see Chapter by Langley-Evans).

Finally, whilst differences in conscious blood pressure between animal groups can be reflected in anaesthetised measurements,[28-33] albeit at lower pressures in general, anaesthetised blood pressure is a poor indicator of conscious blood pressure since anaesthetic depth can be arbitrarily set. Thus the limitations of each technique with each animal model must be taken into consideration to prevent false positives and false negatives in the hypertensive programming effect of particular intrauterine stimuli.

Nutrition

Maternal dietary manipulation has been demonstrated in many animal studies to programme arterial pressure. Perturbations such as maternal under-nutrition (total calorie), restriction in specific dietary components (protein, vitamins, minerals), or restricting placental function (decreased uterine blood flow reducing both nutrient and oxygen availability) lead to elevated blood pressure in progeny across many species (see Chapter by Langley-Evans). In models of under-nutrition, it has been suggested that the programming of hypertension is mediated by glucocorticoid-induced endocrine changes.[5,8,34] Over-nutrition (lard, sodium) has also been reported to programme hypertension.[11,35,36] In some cases it is apparent that maternal diets both low or high in a particular nutrient (calcium,[37] sodium[35,38]) can programme adult hypertension. It is interesting to speculate whether these nutrients act by stimulation or suppression of the same pathway or whether they are acting independently via alternate mechanisms. Importantly, increasing evidence demonstrates that hypertension can occur without impaired fetal growth,[21,39] conversely intrauterine growth restriction does not always result in high adult blood pressure.[40]

Anaemia during Pregnancy

Of particular clinical import are studies examining the influence of diets low in iron. A physiological drop in haemagloblin (to ~100 g/l) occurs in normal pregnancy, due to the increase in plasma volume. However, it has been shown that iron deficiency (70-100 g/l) occurs in ~20% of pregnancies in 'first-world' countries, and up to 75% of pregnancies in developing

countries.[41] Three groups have now demonstrated that iron deficiency induced prior to, and continued throughout, pregnancy in rats leads to intrauterine growth restriction and elevated arterial pressures in the offspring.[42-45] By cross-fostering all pups onto to control fed dams at birth, Gambling et al[44] confirmed that the elevated blood pressure was the result of the iron deficiency in utero and not due to continued iron deficiency during lactation. Interestingly, these elevated adult pressures were preceded by relative hypotension in the early post-weaning period, particularly in females.[42,44] The mechanisms by which intrauterine iron deficiency translates to adult hypertension are as yet unclear, however a reduced nephron endowment has been implicated.[45] It is yet to be determined whether the programming of hypertension by iron deficiency in utero is independent of a generalised effect on intrauterine growth retardation.

Hypertension during Pregnancy

Another condition common during pregnancy is hypertension.[46] It has been predicted that the incidence of chronic hypertension will increase from 1 to 5 in 100 pregnancies over the next decade.[47] This is due to the shift to an older child bearing age in women and the increased risk of hypertension in this older population.[48] However, few studies have followed the children of mothers with hypertension into adulthood,[49-51] though both low-birth weight and macrosomic babies have been linked with mild maternal hypertension.[50,52] Thus, the question of whether chronic hypertension during pregnancy exposes the fetus to an increased risk of developing hypertension and cardiovascular disease later in life is an important one.

Several animal studies have examined the influence of chronic hypertension on fetal development and adult blood pressure. Denton et al[53] published the first study to demonstrate that maternal secondary hypertension could programme hypertension in offspring. In a rabbit model of chronic maternal hypertension, induced using a two-kidney, one-wrapped model of perinephritic hypertension, it was demonstrated that offspring were hypertensive as adults (Fig. 2). The increase in blood pressure only occurred in adult female offspring, though the variation in

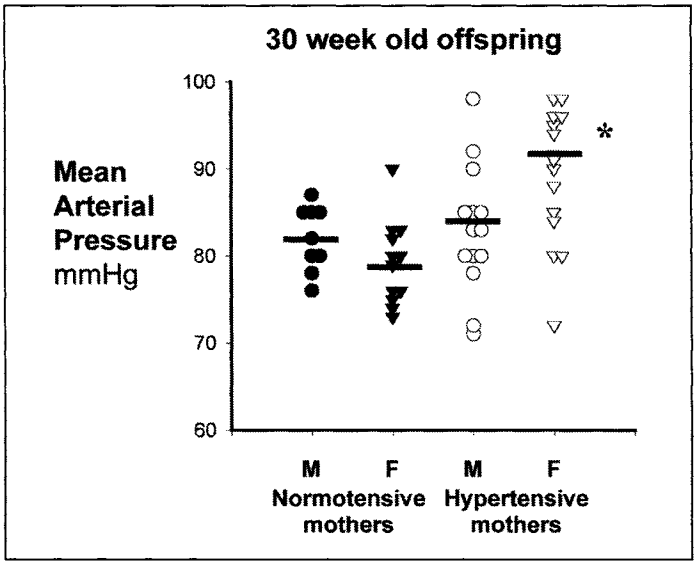

Figure 2. Conscious mean arterial pressure measured at 30 weeks of age in offspring of hypertensive and normotensive rabbit mothers. Individual data presented for male (M, circles) and female (F, triangles). The bars represent the group average. Hypertensive mothers: open symbols; n = 6 mothers; 14 male, 14 female offspring. Normotensive mothers: solid symbols; n = 6; mothers; 9 male, 12 female offspring. * $P < 0.05$ compared to normotensive control.

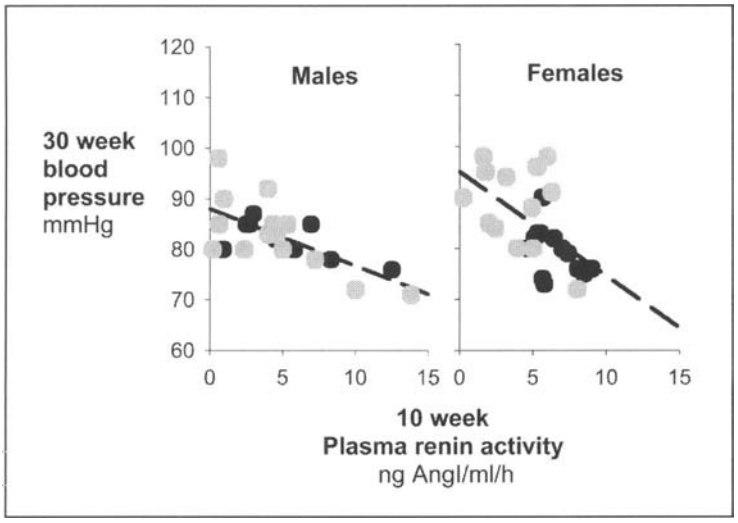

Figure 3. Relationship between plasma renin activity at 10 weeks of age (adolescent) and arterial blood pressure at 30 weeks of age (adult) measured in conscious individual male and female rabbits born of hypertensive (grey) or normotensive (black) mothers. Male offspring R^2 = 0.48, $P < 0.001$; Female offspring $R^2 = 0.31$, $P < 0.005$.

blood pressure in male offspring was increased (Fig. 2). The renin-angiotensin system (RAS) was implicated in this model with significantly lower plasma renin activities in the female offspring of hypertensive mothers at 10 weeks of age (adolescence), prior to any rise in blood pressure. Indeed, plasma renin activity at 10 weeks of age was found to directly correlate with adult blood pressure at thirty weeks of age (Fig. 3). It has been suggested that low plasma renin activity may reflect a reduction in nephron number, which is linked to the development of hypertension.[54,55]

In agreement with the study by Denton and collegues,[53] male offspring of one-kidney, one-clip hypertensive dams also showed no rise in arterial pressure.[56] Interestingly, these male pups were found to be more susceptible to DOCA-salt treatment.[56] These studies suggest that chronic hypertension during pregnancy differentially influences programming in the sexes, an effect documented previously in other models.[38,57-59] In contrast, no effect of increased maternal blood pressure on offspring was demonstrated when blood pressure was increased by central administration of aldosterone,[60] leading to the suggestion that it may not be maternal arterial pressure per se that is responsible for the programming of hypertension in offspring. There is little doubt that the changes in the maternal environment during hypertension, of whatever cause, are complex and thus the stimuli impacting on the fetus may be multifactorial.

In the rabbit model of maternal hypertension discussed above, there a number of possible maternal stimuli that might affect fetal development. Not only was arterial pressure increased but plasma renin activity was also elevated,[53] suggesting that both angiotensin II (AngII) and aldosterone levels in the mothers were elevated during pregnancy.[61,62] Aldosterone can cross the placenta and may possibly have a direct effect on fetal development.[63] Maintenance and growth of the placenta is essential for the normal growth and wellbeing of the developing fetus. The uteroplacental circulation has a local renin-angiotensin system (RAS) that plays important roles in placental angiogenesis and in modulating placental production of cytokines, growth factors and vasoactive substances, which also influence fetal development.[64] Chronic infusion of AngII to pregnant rabbits[65] and ewes[66] has been shown to decrease uterine blood flow and

evidence suggests that uteroplacental perfusion is reduced in humans and animal models with chronic hypertension.[49,67,68] Normally, during pregnancy the uterine artery is particularly insensitive to AngII due to the predominance of angiotensin type 2 receptors (AT_2R),[69] however, uterine artery AT_2R density decreases with chronic AngII.[66] Thus, uterine blood flow may be reduced via this mechanism in pregnancy when maternal plasma AngII levels are increased, affecting placental nutrient transfer. In cultured human placental cells AngII has been shown to decrease 11-beta-hydroxysteriod dehydrogenase type-2 (11β-HSD_2).[70] If 11β-HSD_2 is decreased in mild chronic hypertension, maternal glucocorticoids may cross the placenta and influence organs/systems in the fetus. Another possible contributor to fetal programming of hypertension in this model is maternal renal function which may be compromised,[61,62,71] possibly altering maternal plasma levels of sodium, potassium or urea which may influence fetal development.[72]

Glucocorticoids

Glucocorticoids are potent regulators of fetal growth and development. Mechanisms that tightly regulate fetal glucocorticoid exposure are of considerable importance, as certain organs (kidney, brain) are adversely affected by excess glucocorticoids. Placental 11β-HSD_2 reduces trans-placental passage of maternal glucocorticoids to the fetus, thus protecting the fetus from the deleterious effects of maternal glucocorticoids. Many studies have observed the effect of glucocorticoids to programme high blood pressure in sheep and rat models using either prenatal exposure to stress (e.g., restraint) or infusions of cortisol, corticosterone, ACTH or dexamethasone.[34,73] Prenatal glucocorticoid exposure, induced by blocking placental inactivation of endogenous glucocorticoids, also leads to high blood pressure in adult rats.[19,74] Importantly, it has been shown reproducibly in sheep, that elevated arterial pressure in adults can be programmed in both female and male adult offspring by as little as 2 days of exposure to glucocorticoids at days 26-28 of the 150 day gestation.[75,76] A similar critical window, during the earliest stages of metanephric development, has also been demonstrated in rats.[39,77-79] Glucocorticoid exposure at this critical stage in kidney development also causes high blood pressure in adult rat progeny without affecting birth weight.[39,78] In contrast, glucocorticoid treatment late in gestation does not result in subsequent hypertension.[78,80]

Possible Mechanisms Leading to Adult Hypertension

The cardiovascular system regulates blood pressure to maintain an adequate perfusion to meet the needs of each tissue (Figs. 1, 4). "Normal" blood pressure is regulated by a number of organs and physiological systems, exerting both short (reflex) and long-term effects. Mechanisms integrating the control of arterial blood pressure are outlined and possible adaptations in the development of components of the cardiovascular system resulting in alterations in function and the programming of hypertension have been summarised in Figure 4. A caveat that should be considered when examining the mechanisms underlying the programming of hypertension is whether such changes are present before the onset of hypertension or occur as a consequence of the hypertension. Thus ideally, the mechanisms controlling blood pressure should be examined prior to the establishment of chronic hypertension since compensatory mechanisms might confound interpretation of the results once hypertension has developed.

Long-term blood pressure regulation is inextricably linked to renal excretory function,[81,82] and there is also strong evidence linking the renal actions of the RAS and the sympathetic nervous system to adult hypertension.[83-85] However, the initial stimulus for hypertension to develop need not originate in the kidney. Thus a stimulus from other organs or systems involved in cardiovascular homeostasis, such as altered central sympathetic out-flow, myocardial function or vascular reactivity, may trigger a shift in renal function and an increase in arterial pressure. Thus while the kidney has received the bulk of attention, these other organs and systems need also to be considered in the effort to determine the mechanisms behind developmental programming of hypertension (Figs. 1, 4).

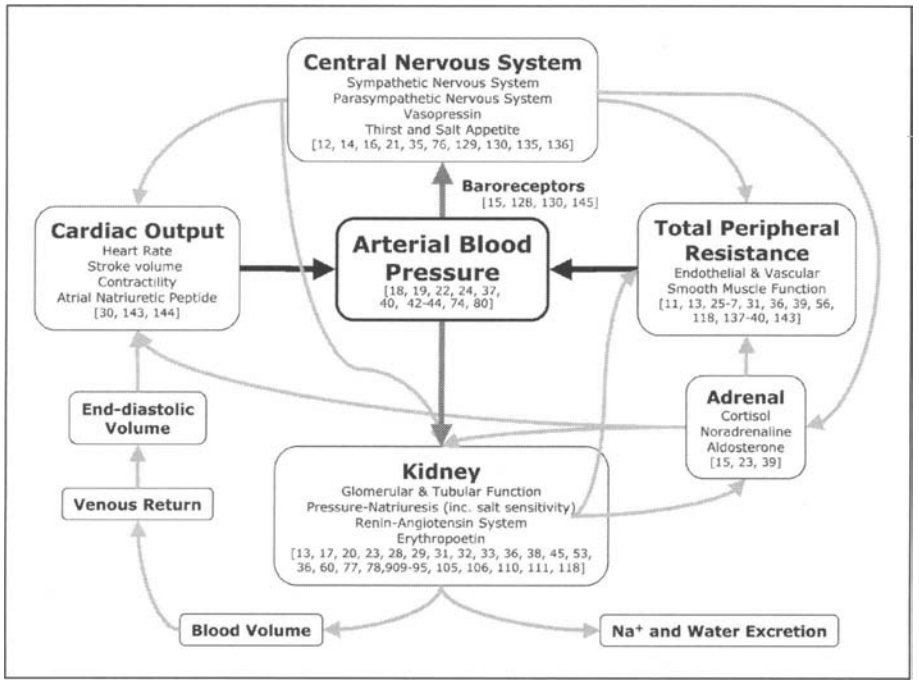

Figure 4. Diagram showing the basic mechanisms controlling blood pressure. Arterial pressure is the product of cardiac output and total peripheral resistance, changes in blood pressure are sensed primarily by the central nervous system and kidneys (red arrows) and mechanisms are activated (grey arrows) that restore blood pressure to "normal". Programming in utero may affect blood pressure by altering the cardiovascular system at any point in this loop. Possible mechanisms are suggested in italics and studies that have examined some of these are cited.

Kidney

The kidney, as stated above, plays a very important role in the control of blood pressure due to its influence on salt and water excretion and thus plasma volume.[81,82] Considerable attention has therefore been directed towards the kidney to look for changes in fetal kidney development and alterations in adult renal structure and function. Disruption of kidney development, due to a programming effect, may permanently alter normal function. Compensatory mechanisms may ensue resulting in hypertension. Where available, the evidence implicating these mechanisms as possible contributors to programming adult hypertension are discussed.

Reduced Nephron Number in Models of Programmed Hypertension

Investigations have focused on nephron development due to the hypothesis advanced by Brenner and colleagues that nephron endowment at birth is inversely related to the risk of developing essential hypertension in later life.[54,55,86,87] In brief, it is postulated that a low nephron number at birth signifies a reduction in total kidney filtration surface area, which is not adequate to meet the demands of the growing animal, with resultant sodium retention.[54,55] Further to this, compensatory mechanisms cause arterial and glomerular hypertension leading to hyperfiltration, a vicious cycle then ensues as the increased work load placed on each nephron causes glomerular sclerosis and further loss of nephron function.[54,55] Reduced nephron number has been documented in a number of animal models of programmed hypertension,

including food restriction, uterine artery ligation, low protein diet, iron deficiency, and glucocorticoid treatment (see ref. 86). Glomerular number has yet to be measured in a number of models of programmed hypertension (chronic hypertension[53]) and blood pressure has yet to be measured in some models known to programme reduced nephron endowment (vitamin A,[88] hyperglycemia[89]). Studies examining the mechanisms whereby a reduction in nephron number may be programmed in utero are discussed elsewhere in greater detail (see Moritz & Cullen-McEwen).

Studies in models with reduced nephron number in which glomerular filtration rate has been measured all show evidence that the remaining nephrons are hyperfiltering.[17,20,29,33,78,90-92] Altered expression of components of the RAS have also been documented in the adult as well as the fetus in these models, suggesting that not only has the developmental role of the RAS been altered, but that the functionality of the system in the adult may have been reset.[17,76,90,93-95] It has been speculated that failure to suppress intrarenal AngII activity during chronic salt loading may lead to salt-sensitive hypertension.[96] Certainly, salt-sensitive hypertension has been demonstrated in offspring of mothers fed a low protein diet, which had previously been shown to have reduced renin expression and indeed fewer nephrons.[93,95]

As a result of this hypothesis, attention has also centred on alterations in the expression of components of the RAS due to this systems prominent role in renal development and its importance in regulating blood pressure in the adult.[81,97,98] Impetus for this direction of research has also been fuelled by the clinical correlate that growth retarded infants, which are prone to later hypertension,[99] have particularly small kidneys, have elevated cord blood renin and AngII concentrations[100,101] as well as elevated renin gene expression in the kidney,[102] suggesting that intra-renal RAS activity may be elevated.

When taken in context with other studies in humans or in experimental animal models, in which hypertension resulted when nephrogenesis was impaired, it is highly suggestive that a kidney abnormality is an essential part of the etiology of the subsequent hypertension.[103,104] However, there is also evidence to suggest that reduced nephron endowment and hypertension may be coincident.[18,87,105] A study has shown that dietary supplements given in combination with a low protein diet can prevent low nephron number without affecting the development of hypertension in the adult.[18,87] Furthermore, reduced nephron number has been documented in the absence of hypertension[105] and programmed hypertension has been demonstrated in the absence of changes in nephron number.[106] Perhaps programmed hypertension is more than reduced nephron number, and compensatory changes in tubular function and/or renal hormonal systems must occur concomitantly for hypertension to develop. These are important questions, awaiting confirmation in future studies.

Tubular Epithelial Sodium Co-Transporters and Hypertension

Programming of epithelial sodium transporters in the renal tubules offer another mechanism by which sodium retention may cause adult hypertension. These transporters are localised to specific segments of the nephron and mediate sodium entry across the apical membrane. These include the Na/H exchanger of the proximal tubule, the Na/K/2Cl co-transporter of the thick ascending limb of Henle, the Na/Cl co-transporter of the distal convoluted tubule, and the α, β, γ-subunits of the epithelial sodium channel (ENaC) of the distal tubule and the collecting duct.[107] Whilst the bulk of the reabsorption of sodium is carried out in the proximal tubule of the nephron, the fine control of sodium reabsorption is carried out in the distal nephron and collecting duct.[108,109] Gene-targeted studies in mice have lead to the suggestion that it is in these later segments of the tubule, downstream to the macula densa, in which sodium delivery is not monitored, that changes in sodium transport play a key role in controlling sodium balance and blood pressure.[108,109] For example, while an increase in the Na/H exchanger in the proximal tubule can be compensated for by other later segments of the tubule, an increase in ENaC activity in the collecting duct, as found in Liddle's syndrome, results in excess sodium reabsorption and hypertension.[107-109]

Few studies have directly examined renal sodium transporters in models of programmed hypertension. One study in 4 week old rats exposed to a low protein diet throughout the second half of gestation, demonstrated up-regulation (at both the mRNA and protein level) of Na/K/2Cl cotransporter of the thick ascending limb of Henle (302% compared to controls) and the Na/Cl cotransporter of the distal convoluted tubule (160% compared to controls).[110] Thus in this model, before the hypertension becomes manifest, the fetal kidney was programmed to inappropriately retain sodium, a finding consistent with the hypothesis that sodium retention might directly contribute to the development of hypertension. Subsequently, the same authors showed that sodium transporters were not down-regulated after hypertension became manifest at 8 weeks of age.[110] This finding is particularly important since it is known that down-regulation of the Na/Cl cotransporter of the distal convoluted tubule is an important component of the pressure-natriuresis response, the crucial mechanism in long-term blood pressure control.[111] Another study, examining the effects of maternal hypercholesterolemia on offspring, demonstrated an increase in Na^+/K^+-ATPase activity in the outer medulla associated with reduced creatinine clearance (estimate of glomerular filtration rate) but not hypertension, though blood pressure was measured in anaesthetised animals and needs to be confirmed.[33] Further studies are required to examine the possibility that prenatal programming of renal epithelial sodium cotransporters can lead to hypertension in the adult.

Other Renal Mechanisms

There are other renal mechanisms controlling blood pressure that should also be considered when examining possible mechanisms leading to programming of adult hypertension. For example, it has been proposed that hypertension may be caused by structural changes that narrow intrarenal blood vessels, increasing preglomerular vascular resistance and the aortic-glomerular capillary pressure gradient.[112] Such a situation present in spontaneously hypertensive rats, and analogous to renal artery stenosis, would result in a cascade of events, including activation of the RAS, leading to hypertension.[112] Whilst pro-hypertensive vascular structural changes have not been investigated specifically in models of programmed hypertension, in sheep exposed to dexamethasone during early gestation accumulation of collagen in the tubular interstitium and peri-adventitia of renal cortical vessels has been demonstrated.[113]

Programming of the sympathetic nervous system has been demonstrated[114] and there is strong evidence implicating increased renal sympathetic activity in the pathogenesis of essential hypertension.[84] Developmentally, growth of the renal nerves is closely linked to the fetal RAS, specifically the timing of renal innervation of the vessels is concomitant with the regression of renin expression along the vasculature.[115] Nerve growth factors are expressed in the fetal kidney and are inducers of differentiation and survival of nerves,[116] thus altered expression of these factors may lead to hyper-innervation of the renal vasculature, an affect which is pro-hypertensive.[84] A few studies have demonstrated alterations in sympathetic function in models of sub-optimal maternal environments. In chick embryos, chronic moderate hypoxia leads to hyper-innervation of the arterial vasculature.[117] In a model of uterine artery ligation increased sympathetic nervous system activity was observed in female rats at 3 months of age, though this was not associated with hypertension.[12] In a model of prenatal stress in rats, adrenoreceptor responses were altered in renal, but not femoral, mesenteric or saphenous arteries.[118] Additional tests led to the conclusion that the enhanced responsiveness to phenylephrine was due to alterations in signal transduction not increased nerve or receptor densities.[118]

No one to date has examined the intrinsic renal mechanisms that maintain glomerular filtration rate, the first step in sodium excretion, constant: tubulo-glomerular feedback, the myogenic response or the phenomenon of pressure-natriuresis. Resetting of these mechanisms due to alterations in hormone sensitivity be it due to increased receptor density, increased hormone availability or up-regulation of second messenger systems has yet to be studied. Interestingly, however, human data has suggested that the pressure-natriuresis relationship is influenced by birth weight.[119] In the future, attention should also focus on

sex-related programming effects on renal structure and function given the striking differences in renal function previously reported for healthy males and females.[59,120,121]

Brain

The central nervous system also plays a major role in maintaining body fluid homeostasis via sympathetic stimulation, vasopressin release and increase in salt and water appetite. For example, the hypothalamus is involved in fluid balance through salt and water intake and control of sympathetic drive,[122,123] while the medulla oblongata affects cardiovascular function, mainly through the control of peripheral sympathetic drive, including baroreflexes.[123,124] The lamina terminalis is situated in the anterior wall of the third ventricle and consists of the median preoptic nucleus and the circumventricular organs; the subfornical organ and the organum vasculosum. This region of the brain has a crucial role in osmoregulatory vasopressin secretion and thirst.[125] There is a local brain RAS and hyperactivity of this system has been implicated in the development and maintenance of hypertension. Confirmation of the role of the central RAS and its effects on blood pressure and fluid balance has been obtained using transgenic mouse models that selectively over-express components of the RAS within the brain.[126,127] Other signalling systems (i.e., noradrenergic or glutaminergic) in brain regions involved in cardiovascular control may also be implicated in the fetal programming of adult hypertension, but have yet to be considered (see ref. 123).

Evidence of Altered Brain RAS in Models of Programmed Hypertension

To date, there are only a few studies in the literature that suggest a link between altered brain RAS, as a result of exposure to a sub-optimal intrauterine environment, and adult hypertension.[35,128,129] Studies have demonstrated an up-regulation of AT_1 receptors in the medulla oblongata and higher expression of angiotensinogen in the hypothalamus of late gestational fetuses, previously exposed to dexamethasone at the end of the first month of pregnancy.[129] This increase in AT_1 receptors expression of the medulla oblongata persisted in adult sheep measured at 7 years of age, when high blood pressure was clearly evident.[129] A recent study of 1 year-old lambs exposed to maternal under-nutrition (50% of daily intake) from day 1-30 of gestation, demonstrated blunted baroreflex sensitivity during AngII infusion.[128] Similarly, rats of low-protein fed mothers had increased blood pressure and demonstrated altered baroreflex function.[130] The hypertension of these offspring was significantly attenuated by intracerebroventicular administration of an AngII antagonist.[130] Further, Swenson et al showed that the hypertension of 30-day old rats subjected to a high-salt diet throughout gestation and the post-natal period, was partly due to increased brain AT_1 receptor activation.[35] Taken together, these studies suggest that increased AngII action within cardiovascular control centres in the brain contribute to programmed hypertension.[35,128-130] it is important to bear in mind that resetting of the baroreflex is found, commonly, as a consequence of developed hypertension.[131] However, in some strains of rats (spontaneously hypertensive rats, Dahl salt-sensitive rats) abnormal baroreflex function precedes the development of hypertension and may very well be the cause rather than the consequence of hypertension.[132,133]

Research also supports the hypothesis that salt appetite and thirst can be programmed in utero (see ref. 134). In a study in sheep, maternal dehydration during late gestation, has been demonstrated to programme hypertension.[135] Further, this study demonstrated that the offspring of water-restricted ewes had increased plasma osmolality, hematocrit and threshold for AVP secretion.[135] In another study, in which extracellular dehydration and exaggerated sodium appetite was produced in pregnant rats by polyethylene glycol treatment, salt appetite of offspring was increased.[136]

Heart and Vasculature

Adaptations in the cardiovascular system are linked to the development and maintenance of systemic hypertension. Alterations in myocardial, conduit and resistance artery geometry and

reactivity will have a direct impact on cardiac output and total peripheral resistance, the primary determinants of arterial pressure (see Fig. 4). However, little is known of the role of the cardiovascular system in the translation of intrautero insults into a chronic elevation of arterial pressure in the adult. Of the limited studies available, vascular dysfunction of both the conduit and/or resistance vasculature is a common feature, though the responses vary from study to study due to differences in vessel size (conduit or resistance), vascular bed, gender, intrauterine insult, and age of offspring at time of examination.

Vasculature

The primary vascular defect identified in studies to date, appears to be an impaired endothelium-dependent relaxation and this has been demonstrated in offspring with hypertension induced by various adverse intra-uterine events including undernutrition,[26,137] protein restriction,[25] high fat intake[11,138] and placental insufficiency.[139,140] The precise nature of the defect underlying the reduced endothelium-dependent dilation is of considerable conjecture but includes impaired synthesis of NO,[26,139] and/or impaired response of the vascular smooth muscle cells to NO,[27,140] Whilst not a consistent finding, some studies have demonstrated an increased responsiveness to vasoconstrictors, though the effect is not universal to constrictors in general, even within the same study.[11,26,137-139] This increased responsiveness is likely the result of impaired buffering by endothelial factors,[139] however the contribution of increased numbers of specific receptor types mediating vasoconstriction cannot be rule out (see Poston).

Heart

Intrauterine insults such as anaemia and hypoxemia have been shown to have significant effects on the fetal heart.[30,141,142] However, few studies have examined the consequences of these stimuli during fetal life on the adult. In one interesting study, in a model of perinatal anaemia, evidence of coronary vascular remodelling has been described in adult sheep, in which maximal coronary conductance and reserve increased, providing a physiological advantage.[30,143] Whilst maternal dexamethasone exposure led to hypertension and increased cardiac output in 7 year old offspring, associated ventricular hypertrophy and reduced cardiac functional reserve, these changes are likely due to secondary effects of the hypertension.[144,145] Further studies performing detailed analysis of the structure and function of hearts in juvenile and adult offspring, subjected to an adverse intrauterine environment, are required.

Conclusions

Strong evidence in both human and in animal studies supports the hypothesis that hypertension can be programmed in utero. Future studies should encompass the following: (1) Prehypertensive animals should be studied to differentiate between the primary initiating programming events and events secondary to the consequent development of hypertension. (2) Best practice methods should be employed to determine arterial blood pressure; single time-point measures are open to misinterpretation particularly in young restrained animals. (3) It is unlikely that the interventions (i.e., under-nutrition, glucocorticoids) used to programme hypertension affect single organs but will rather affect multiple organs or systems (i.e., programming of RAS may alter brain, heart and kidney function), unless adverse stimuli are restricted to narrow windows in the timing of development. Thus, the reductionist approach of examining single organs or systems will not provide a complete picture of the physiological adaptations that have taken place. (4) Furthermore, accumulating evidence demonstrating sexually dimorphic programming in response to an adverse maternal environment highlights the need to consider male and female offspring separately. Understanding the mechanisms involved in the programming of hypertension will be essential for devising preventative and/or treatment strategies.

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